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Diabetes mellitus, diabetes insipidus, optic atrophy, and deafness: A case of Wolfram (DIDMOAD) syndrome

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Abstract

Purpose: To report a case of Wolfram syndrome (WS) characterized by diabetes mellitus, diabetes insipidus, progressive optic atrophy, and deafness.
Case report: A 19-year-old female patient, a known case of diabetes mellitus type I from six years before, presented with progressive vision loss since four years earlier. On fundoscopic examination, she had bilateral optic atrophy without diabetic retinopathy. The patient also had diabetes insipidus, neurosensory deafness, and neurogenic bladder.
Conclusion: WS should be considered a differential diagnosis in patients with diabetes mellitus who present with optic atrophy, and it is necessary to perform a hearing test as well as collecting 24-h urine output.

Keywords: Diabetes mellitus; Diabetes insipidus; Optic atrophy; Deafness

Introduction

Wolfram syndrome (WS) is an autosomal recessive neurodegenerative disorder characterized by Diabetes Insipidus, Diabetes Mellitus (non-autoimmune), Optic Atrophy, and Deafness (a set of conditions referred to as DIDMOAD).[1–3] The gene responsible for the WS, named WSF1, encodes an endoplasmic reticulum membrane-embedded protein called wolframin that is expressed in pancreatic beta cells and neurons.[4–6] The estimated prevalence of WS is 1 in 770,000, and it is believed to occur in 1 of 150 patients with type 1 diabetes.[6] Affected patients usually develop insulin-requiring diabetes and optic atrophy in early childhood, and diabetes insipidus as they become teenagers or young adults. In WS patients with diabetes insipidus, not only does vasopressin neuron loss occur in the supraoptic nucleus, but there is also a defect in vasopressin precursor processing.[7] Anterior pituitary dysfunction has also been reported.[6] Other manifestations of WS include progressive sensorineural deafness, hydronephrosis (due in part to the high urine flow in diabetes insipidus), and neurologic dysfunction.[8] Why severe insulin-requiring diabetes develops is not known; immunologic factors do not appear to be important.[3] Affected individuals have a median life expectancy of 30 years, with early mortality credited to neurological disorders, urological abnormalities and infection.[9] There is currently no cure for WS. Differential diagnosis and treatment are difficult due to the variable presentation of symptoms.[10] In the present study, we report one patient with WS from Ardabil, Iran.

Case presentation

A 19-year-old female patient, a known case of type I diabetes mellitus from six years before, presented to a private ophthalmology office. She complained of progressive

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vision loss from four years earlier. Her visual acuity reduced to 1/10 on both eyes. She had a history of nocturia and high urine output for five years, and after that, she had incontinency. In the previous two years, she had been avoiding difficulty and using self-intermittent catheterization four times a day.

On ophthalmic examination, intraocular pressure was 15 mmHg in both eyes, and biomicroscopic examinations were completely normal. On fundoscopic examination, she had bilateral optic atrophy without diabetic retinopathy (Figs. 1 and 2). Accordingly, WS was suspected by the ophthalmologist, who referred her to an endocrinologist.

Investigations revealed polyuria (14 L per day), hypernatremia (156 mEq/L), and hyperglycemia (351 mg/dL). Other laboratory values were: creatinine, 1.1 mg/dL; urea nitrogen, 28 mg/dL; K, 4.5 mEq/L; TSH, 2.5 mU/L. A random urine analysis showed a urine specific gravity of 1.006, and the results of 24-h urine collection obtained a urine specific gravity of 1.005 [normal values: 1.010–1.030]. It was suspected that there might be an underlying cause for diabetes insipidus, due to the presence of a low urine specific gravity … Subsequently, a urine and plasma osmolality was performed, which were 150 and 312 mmol/kg, respectively. These findings suggested a disturbance in the regulation of vasopressin. Therefore, a standardized water deprivation test was done. There was no change either in urine specific gravity or urine osmolality before and after the water deprivation test. After nasal desmopressin administration, urine osmolality increased from 125 mOsm/kg to 600 mOsm/kg and serum osmolality increased from 281 mOsm/kg to 328Osm/kg. Given to an increase in urine osmolality of more than 100% measured by the desmopression stimulation test, the patient was diagnosed with complete central diabetes insipidus. Treatment with oral desmopressin was prescribed 100 mcg three times daily. A few days later, the volume of urine collected in 24 h was within acceptable range. A Magnetic Resonance Imaging (MRI) of the brain revealed the loss of the physiological hyperintense signal of the posterior pituitary gland (bright spot) on T1-weighted images, suggesting the diagnosis of central diabetes insipidus (Fig. 3).

Fig. 1. Optic atrophy without diabetic retinopathy in the right eye.

Fig. 2. Optic atrophy without diabetic retinopathy in the left eye.

An audiologic examination revealed neurosensory deafness, and audiometry showed a bilateral high-frequency sensorineural hearing loss. Renal sonography showed pelvicalyceal dilatation in both kidneys, equal to hydronephrosis grade II. The bladder wall had a trabecular pattern, and the urinary tract was dilated on both sides. The patient had 150 ml post-voiding bladder residue. Urologic examination and sonographic findings were consistent with a neurogenic bladder.

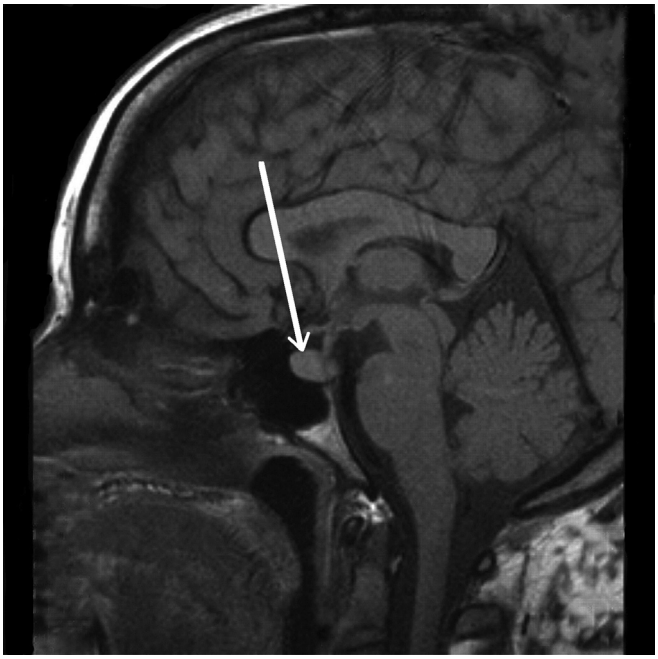

Fig. 3. Magnetic Resonance Imaging (MRI) of the brain revealed the loss of posterior pituitary bright spot, suggesting the diagnosis of central diabetes insipidus.

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The patient's sister had similar symptoms, but she did not cooperate for further evaluation.

Discussion

WS was first described in 1938 by Wolfram and Wagener[11] as a hereditary syndrome characterized by diabetes mellitus and optic atrophy acquired early in life. Subsequent reports added diabetes insipidus and deafness to the syndrome, which develop in approximately 73 and 62% of sufferers, respectively.[3,12]

The minimal criteria for diagnosis are juvenile-onset diabetes and optic atrophy; however patients also present with additional complications, hence the acronym DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness) is used. The diagnostic criteria for WS are shown in Table 1. The diagnosis is established in individuals of all ages in whom two pathological WFS1 or CISD2 mutations are identified.[13]

Diabetes mellitus is a key feature of WS, which is usually the first sign of the disease (median age at diagnosis, 6–15 years), and optic atrophy (median age at diagnosis 11 years). The mean age of presentation of diabetes mellitus has been reported to be 5 ± 4 years.[14] There are multiple differences between the presentation and course of autoimmune Type 1 diabetes and diabetes of WS. Namely, patients affected with WS have a low incidence of diabetic ketoacidosis at the time of diagnosis (only 3% compared to 30% in Type 1 diabetes), a much lower insulin requirement in the first several years after diagnosis, rare microvascular complications, and rare presence of diabetes antibodies.[15] Patients with WS show smaller glycemic variability than individuals with type 1 diabetes mellitus, and this may be associated with persistent residual insulin secretion.[16]

Diabetes insipidus is another component of WS. A loss of vasopressin-producing neurons in the hypothalamus has been well documented in this disease and is thought to be the cause of WS-associated diabetes insipidus.[17,18] Neuroradiologists have reported a loss of signal intensity in the posterior pituitary, indicating an absence or degeneration of the neurohypophysis[18,19]; some patients have been found to have "empty sella".[20]

Patients with WS demonstrate progressive ophthalmologic symptoms that usually occur after diabetes mellitus. Besides optic atrophy, constriction of visual fields and declined visual acuity and color vision are the other ophthalmological findings in WS[21]; however, diabetic retinopathy is rarely observed.[22] Only five cases with WS have been reported without optic atrophy.[22] In 2002, Al-Till et al[23] performed a study to investigate ophthalmologic abnormalities in fifteen patients with WS. Of 15 patients with WS reviewed in this study, 93.3% had optic atrophy, 92.9% had color deficit, 66.6% had cataract, 30% had pigmentary retinopathy, and 20% had diabetic retinopathy. Abnormal pupillary light reflexes and nystagmus were also reported.[23] In another study, eye complications were described in four patients with WS. The ophthalmic signs were a progressive decrease in visual acuity, constriction of the peripheral visual field with or without central scotoma, color vision disturbances, and bilateral optic disc atrophy. Diabetic retinopathy was a rare complication.[24] Recently, the retinal thinning has been proposed as a marker of disease progression in patients with WS.[25]

Deafness in WS is commonly a high-frequency, symmetric, sensorineural hearing loss, usually manifesting in the second or third decade with a relatively slow rate of deterioration.[26,27] Some studies have reported urinary tract abnormalities (hydroureter, urinary incontinence, recurrent infections) in patients with WS, that these abnormalities are expected in about 66% of patients. Urinary tract abnormalities include obstruction of the ureters, an atonic bladder with a large capacity, high pressure bladder with sphincteric dyssynergia, and incontinence.[28] Urinary tract dilatation is presented in 45% of patients with WS, which may be secondary to chronic high urine flow rate or neurodegeneration in different levels of the urinary tract.[29]

Differential diagnosis of WS includes[13]: (1) Mitochondrial disorders: Maternally Inherited Diabetes mellitus and Deafness, Leber Hereditary Optic Neuropathy; (2) Thiamine-responsive megaloblastic anemia, diabetes, and deafness; (3) Autosomal Dominant Optic Atrophy; (4) X-linked Charcot-Marie-Tooth disease type 5; (5) Deafness, Dystonia, Optic Neuronopathy syndrome; (6) Friedreich ataxia; (7) Bardet-Biedl syndrome; (8) Alstrom syndrome; and (9) Congenital rubella syndrome. The association of diabetes mellitus with optic atrophy also occurs in Friedreich's ataxia, Refsum disease, Alstrom syndrome, Lawrence-Moon syndrome, Kearn-Sayre syndrome, and deafness and diabetes in the"3243" mitochondrial DNA mutation.[30]

The pathogenesis of the disease remains unknown, but genetic linkage studies have shown that the mutations of the WFS1 gene are responsible for the symptoms in 90% of cases

Table 1
The diagnostic criteria for Wolfram syndrome.

Major criteria	Minor criteria	Minimum required	Other variable suggestive evidence:
1. Diabetes mellitus <16 yrs, 2. Optic atrophy <16 yrs	1. Diabetes insipidus, 2. Diabetes mellitus >16 yrs, 3. Optic atrophy >16 yrs, 4. sensorineural deafness, 5. Neurological signs (ataxia, epilepsy, neuropathy, cognitive impairment), 6. Renal tract abnormalities, 7. 1 loss of function mutation in _WFS1/CISD2_ AND/OR family history of Wolfram syndrome	2 major OR 1 major plus 2 minor criteria	- Hypogonadism (males), - Absence of type 1 diabetes auto-antibodies, - Bilateral cataracts, - Psychiatric disorder, - Gastrointestinal disorders

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meeting specific WFS diagnostic criteria. This gene is located on the short arm of chromosome 4 (4p16). The WFS1 gene encodes an 890-amino-acid protein called wolframin, a putative multispanning membrane glycoprotein of the endoplasmic reticulum.[31] Although no function has yet been ascribed to wolframin; however, its localization to the endoplasmic reticulum suggests it can play a role in calcium homeostasis, membrane trafficking and protein processing.[32]

There is currently no cure for WS, but there are treatments for some of the features. Diabetes mellitus is treated with insulin, and diabetes insipidus with vasopressin. While hearing aids can help with hearing loss, there is unfortunately no treatment for vision loss. Renal problems may be treated by catheterization (passing a thin, flexible tube into the bladder to drain away urine), and some of the neurological symptoms can be treated with medication.[29]

Based on the findings of the present case, it is highly recommended that, in patients with diabetes mellitus who have optimal blood sugar presenting with polyuria and polydipsia, we need to do urine specific gravity to prove the presence of diabetes insipidus. In such patients, performing an ophthalmologic evaluation can probably reveal this rare disorder of Wolfram syndrome. In addition, ophthalmologists should be aware that in patients presenting with diabetes mellitus and optic atrophy without any signs of diabetic retinopathy, it is necessary to perform a hearing test as well as collect and analyze 24-h urine output. Thus, awareness of this condition and timely diagnosis is important for improving patient prognosis, anticipating associated complications, and enabling timely genetic counseling for family members.

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